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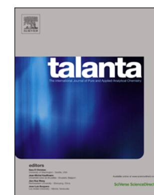

Dispersive solvent-free ultrasound-assisted ionic liquid dispersive liquid–liquid microextraction coupled with HPLC for determination of ulipristal acetate

Aiqin Gong [a,b], Xiashi Zhu [a,*]

[a] College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China
[b] Yangzhou Polytechnic Institute, Yangzhou 225127, China

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ABSTRACT

In this paper, a simple and efficient ultrasound-assisted ionic liquid dispersive liquid–liquid microextraction (UA IL-DLLME) coupled with high-performance liquid chromatography for the analysis of ulipristal acetate (UPA) was developed. UPA could be easily migrated into 1-octyl-3-methylimidazolium hexafluorophosphate [C_8mimPF_6] IL phase without dispersive solvent. The research of extraction mechanism showed that hydrophobic interaction force played a key role in the IL-DLLME. Several important parameters affecting the extraction recovery were optimized. Under the optimized conditions, 25-fold enrichment factor was obtained and the limit of detection (LOD) was 6.8 ng mL^{-1} (tablet) or 9.3 ng mL^{-1} (serum) at a signal-to-noise ratio of 3. The calibration curve was linear over the range of 0.03–6.0 μg mL^{-1}. The proposed method was successfully applied to the UPA tablets and the real mice serum samples.

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1. Introduction

Ulipristal acetate [17α-acetoxy-11β-(4-*N*,*N*-dimethyl aminophenyl)-19-norpregna-4,9-diene-3,20-dione] (UPA), a selective progesterone receptor modulator (Fig. 1), can prevent unintended pregnancy by delaying ovulation for up to five days after contraceptive failure. In August 2010, UPA had gained the FDA's approval for use as an oral emergency contraception tablet in the U.S. with trade name Ella. Until now it is found that Ella may cause serious side effects including abdominal pain, menstrual disorder, headache, nausea and so on [1]. In addition, the study for UPA to treat contraceptive gynecological indications (fibroma uteri, adenomyosis) and Cushing's syndrome is in progress [2]. In view of safe medication and investigating pharmaceutical dynamics of drugs, a simple, sensitive analytical procedure is needed to determine UPA in pharmaceutical formulation and in biological fluids. HPLC has been used to determine UPA in bulk [3]. But to the best of our knowledge, there were few literatures to analyze UPA in biological samples.

An appropriate preconcentration/separation method should be developed due to matrix interference and low concentration of analytes in real biological samples before analysis [4]. In recent years, many preconcentration/separation steps have been oriented toward the fast development of simplification and miniaturization. In particular, the use of alternative non-contaminant and non-toxic solvents instead of high quantities of organic solvents is preferred during preconcentration/separation. Solid phase microextraction (SPME) and liquid phase microextraction (LPME) have been extensively used to preconcentration/separation analytes in complex matrix with their high ability of sample clean up and analyte preconcentration, and low consumption of solvents. SPME would required a specific device loaded with certain adsorption material as well as a high-pressure delivery system that would be relatively expensive [4]. Moreover the operation of LPME is simpler and faster than that of SPME (which includes adsorption progress and desorption progress). Dispersive liquid–liquid microextraction (DLLME), developed by Assadi and co-workers in 2006 [5], is a miniaturized form of liquid phase extraction that employs microliter volumes of extraction solvent. Compared with other microextraction techniques, the advantages of DLLME are simplicity of operation, rapidness, accuracy, and it has been extensively applied in drugs analysis [4,6–8].

Extraction solvents (such as tetrachloroethylene [9], chlorobenzene [10] and carbon tetrachloride [11]) and dispersive solvents (such as methanol [12,13], acetone [9,10] and acetonitrile [11,14]) are usually used in DLLME. Because of the relatively high toxicity of these conventional chlorinated extraction solvents, developing environment-friendly "green" extraction solvents has inspired the great interest of examiners. Ionic liquids (IL) has been more and more used as extraction solvent in DLLME (IL-DLLME)

* Corresponding author. Tel./fax: +86 514 7975244.
E-mail addresses: xszhu@yzu.edu.cn, zhuxiashi@sina.com (X. Zhu).

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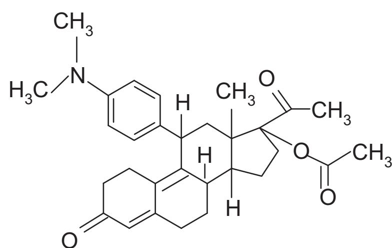

Fig. 1. The structure of ulipristal acetate.

because of its low volatility and low toxicity [4]. Recently ultrasound-assisted (UA) and temperature-controlled (TC) techniques are the most preferred modifications in IL-DLLME [15,16]. However, the technique of dispersive solvent-free UA IL-DLLME has seldom been applied for extraction of drugs in biological samples.

In this paper, hydrophobic IL 1-octyl-3-methylimidazolium hexafluorophosphate [C_8mimPF_6] as extraction solvent of dispersive liquid–liquid microextraction was first time used, which could be completely dispersed into the aqueous sample solution by sonication at 313 K without dispersive solvents, and UPA was easily migrated. The discussion of extraction mechanism showed that hydrophobic interaction force was the main driving force for UPA transfer from water into IL. The proposed method was successfully applied to the real mice serum samples and UPA tablets.

2. Experimental

2.1. Reagents and standards

UPA standard (with purity 99%), UPA tablet (30 mg tablet^{-1}) and blank tablet were kindly provided by Jiangsu Lianhuan Pharmaceutical Co., Ltd (Jiangsu, China). Methanol, ethanol, acetonitrile, acetone, ammonia, ammonium chloride, 1-bromobutane, 1-bromohexane, 1-bromooctane and triethylamine were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). 1-methylimidazole was obtained from Shanghai Darui Specialty Chemicals Co.,Ltd (Shanghai, China) and ammonium hexafluorophosphate from Shanghai Bangcheng Chemical Co., Ltd (Shanghai, China). Methanol and acetonitrile were chromatographic grade, 1-methylimidazole was chemical pure, and all other materials were analytical reagent grade and water was distilled, deionised.

UPA stock solution of 2.0 mg mL^{-1} was prepared by dissolving 0.20 g of UPA in 100.0 mL of anhydrous ethanol and kept in coolness and darkness. The stock solution was further diluted with anhydrous ethanol to obtain a standard working solution of 0.10 mg mL^{-1} before using.

2.0 mol L^{-1} NH_3–NH_4Cl buffer solution (pH 8.0) was prepared by dissolving appropriate amounts of ammonium chloride and ammonia.

2.2. Apparatus

The analysis of UPA was carried by a 1200 series liquid chromatography (Agilent Technologies Inc., USA) equipped with photodiode-array detector (PDA). All absorption spectral recordings and absorbance measurements were performed on a UV 2501 spectrophotometer (Shimadzu, Japan). The pH measurements were done by a pH S-25 pH meter (Shanghai, China). A DK-S22 thermostatic water-bath (Shanghai Jinghong Laboratory Instrument Co., Ltd., China) was used to control temperature. A centrifuge Model 80-2 (Shanghai Pudong Physical Optics Instrument Factory, China) was used to accelerate the phase-separation process. The microextraction was assisted by a 40 kHz, 100 W ultrasonic generator (KQ 50E Kunshan Ultrasonic Instrument Co. Ltd., Kunshan, China).

2.3. Analytical method

2.3.1. Sample preparation

For UPA tablet, five tablets of UPA was weighed and crushed, and then sample powder of about one tablet was accurately weighed and placed in a 50 mL of beaker and dissolved with anhydrous ethanol. Insoluble excipient was removed by filtration through a 0.45 μm membrane filter. The filtered solution was diluted to100.0 mL with anhydrous ethanol and kept in coolness and darkness before analysis.

For mice serum, abdominal artery blood samples from mice at different time points were collected into heparinized plastic tubes, upon oral administration of 0, 5, 10, 30 mg UPA of 1 kg healthy mice. After placing them at 310 K water bath for 1 h, mice serum samples were obtained after centrifuging the blood samples. According to the method of Chen et al. [17], to eliminate protein, 1.0 mL of serum samples was placed in a 10 mL glass tube and 4.0 mL of acetonitrile was added. The mixture was shaken for 30 s and centrifuged for 10 min at 3000 rpm. Finally the supernatant was determined for UPA.

2.3.2. Synthesis of IL

[C_4mimPF_6], [C_6mimPF_6] and [C_8mimPF_6] were synthesized according to Ref. [18], using such materials as 1-bromobutane, 1-bromohexane, 1-bromooctane, 1-methylimidazole and ammonium hexafluorophosphate.

2.3.3. Extraction procedure

To a 10.0 mL centrifuge tube, 50.0 μL of [C_8mimPF_6], 1.0 mL of buffer solution (pH=8.0) and adequate UPA standard or sample solutions were added; the solution was diluted to 10.0 mL with distilled water. After shaken, the mixture was ultrasonically extracted for 10 min at 313 K. Then a cloudy mixture was formed. After cooled at 278 K for 15 min, the cloudy solution was centrifuged for 5 min at 2500 rpm and the IL phase was deposited at the bottom of the tube. Then the upper aqueous phase was removed with a syringe. The IL phase was diluted with ethanol to 0.4 mL. The resulting analytical solution was homogenized ultrasonically and filtered with 0.45 μm filter membrane before HPLC analysis.

2.3.4. HPLC measurements

Chromatographic separation of UPA was performed on an Apollp C_{18} column (150 × 4.60 mm, 5 μm) (Evans Trade Co., Ltd, Shanghai, China). The mobile phase was a mixture of methanol and 0.05% triethylamine (90:10, v/v) at a flow rate of 1.0 mL min^{-1}. The injection volume was 10.0 μL and column temperature was kept at 303 K. The monitoring wavelength was 305 nm and reference wavelength and bandwidth were 350 nm and 4 nm, respectively.

2.3.5. Determination of partition ratio

The partition ratio of UPA in ILs (i.e. [C_4mimPF_6], [C_6mimPF_6], [C_8mimPF_6]) and water were determined. The partition ratio $D_{IL/W}$ was calculated according Eq. (1) [19]:

$$D_{IL/W} = \frac{C_i - C_f}{C_f} \times \frac{V_{eq}}{V_{IL}} \quad (1)$$

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